Heterogeneous FDG-guided dose-escalation for locally advanced NSCLC (the NARLAL2 trial): Design and early dosimetric results of a randomized, multi-centre phase-III study

Design and early dosimetric results of a randomized, multi-centre phase-III study

Møller, Ditte Sloth; Nielsen, Tine Bjørn; Brink, Carsten; Hoffmann, Lone; Lutz, Christina Maria; Drøgemüller Lund, Mikkel; Hansen, Olfred; Schytte, Tine; Khalil, Azza Ahmed; Knap, Marianne Marquard

Total number of authors:
17

Published in:
Radiotherapy and Oncology

Link to article, DOI:
10.1016/j.radonc.2017.06.022

Publication date:
2017

Document Version
Peer reviewed version

Heterogeneous FDG-guided dose-escalation for locally advanced NSCLC (the NARLAL2 trial): Design and early dosimetric results of a randomized, multi-centre phase-III study

Ditte Sloth Møller (1), Tine Bjørn Nielsen(2), Carsten Brink(2), Lone Hoffmann(1), Christina Maria Lutz (1), Mikkel Drøgemüller Lund(3), Olfred Hansen(2), Tine Schytte(2), Azza Ahmed Khalil(1), Marianne Marquard Knap(1), Christa Haugaard Nyhus(3), Wiviann Ottosson (4), Patrik Sibolt (4,5), Svetlana Borissova(4), Mirjana Josipovic(6,7), Gitte Persson(6), Ane Lindegaard Appelt(3,8)

1 Department of Oncology, Aarhus University Hospital

2 Laboratory of Radiation Physics and Department of Oncology, Odense University Hospital, Odense, Denmark

3 Department of Oncology, Vejle Hospital, Vejle, Denmark

4 Radiotherapy Research Unit, Department of Oncology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark

5 Center for Nuclear Technologies, Technical University of Denmark, Roskilde, Denmark

6 Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

7 Niels Bohr Institute, University of Copenhagen, Copenhagen, Denmark

8 Leeds Institute of Cancer and Pathology, University of Leeds, and Leeds Cancer Centre, St James's University Hospital, Leeds, UK

Number of pages: 11

Number of tables: 2

Number of figures: 3

Running title: FDG-guided dose-escalation for NSCLC

Key words: NSCLC; Dose-escalation, Randomized phase-III trial

Corresponding author:

Ditte Sloth Møller, PhD

Aarhus University Hospital, Department of Medical Physics

Noerrebrogade 44, building 5J, 2. Floor

8000 Aarhus C, Denmark

Phone: (+45) 78462589

E-mail: dittmoel@rm.dk

Abstract

Background and Purpose

Local recurrence is frequent in locally advanced NSCLC and is primarily located in FDG-avid parts of tumour and lymph nodes. Aiming at improving local control without increasing toxicity, we designed a multi-centre phase-III trial delivering inhomogeneous dose-escalation driven by FDG-avid volumes, while respecting normal tissue constraints and requiring no increase in mean lung dose. Dose-escalation driven by FDG-avid volumes, delivering mean doses of 95Gy(tumour) and 74Gy(lymph nodes), was pursued and compared to standard 66Gy/33F plans.

Material and Methods

Dose plans for the first thirty patients enrolled were analysed. Standard and escalated plans were created for all patients, blinded to randomization, and compared for each patient in terms of the ability to escalate while protecting normal tissue.

Results

The median dose-escalation in FDG-avid areas was 93.9Gy(tumour) and 73.0Gy(lymph nodes). Escalation drove the GTV and CTV to mean doses for the tumour of 87.5Gy(GTV-T) and 81.3Gy(CTV-T) in median. No significant differences in mean dose to lung and heart between standard and escalated were found, but small volumes of e.g. the bronchi received doses between 66-74Gy due to escalation.

Conclusions

FDG-driven inhomogeneous dose-escalation achieves large increment in tumour and lymph node dose, while delivering similar doses to normal tissue as homogenous standard plans.

Introduction

Locally advanced non-small cell lung cancer (LA-NSCLC) lacks effective treatment options. Local control and survival after curative intended radiotherapy (RT) is poor, despite the use of modern intensive chemo-radiotherapy schedules[1]. Several studies have suggested that local control can be improved by increasing the radiation dose[2,3], but the benefit of dose-escalation has been heavily debated after the publication of the RTOG-0617 trial[4]. In RTOG-0617, the entire target volume, including margins, was homogenously escalated, resulting in irradiation of large volumes to high dose levels, including substantial volumes of normal tissue.

An inhomogeneous dose-escalation strategy can alternatively be used to reduce the dose-escalated volume[5,6], allowing adherence to strict dose constraints for vulnerable normal tissues. Studies on relapse patterns have shown good correlation between tumour regions with high ^{18}fluorodeoxyglucose(FDG)-avidity before treatment and loco-regional failures[7,8]. Furthermore, a low frequency of lymph node-only relapse was demonstrated after radical RT[9,10]. This can be used to guide inhomogeneous dose-escalation strategies by delivering high dose guided by the most FDG-PET avid parts of the tumour. The increased toxicity in the dose-escalated arms of RTOG-0617 furthermore suggests that dose-escalation trials should avoid increasing dose to organs at risk (OAR) above the levels reached with current standard RT. This, however, requires strict radiotherapy quality assurance (QA), including careful use of intensity modulated and image guided radiotherapy (IMRT and IGRT)[11].

In RTOG-0617, the 60 Gy schedule was superior to 74 Gy. However, the Danish Oncological Lung Cancer Group (DOLG) conducted a randomized phase-II trial (NARLAL) in which patients with LA-NSCLC received either 60 or 66 Gy, concomitant with oral vinorelbine[12]. Both arms were well tolerated and the 66 Gy arm was chosen as the preferred arm in a pick-the-winner design.

Based on these considerations, DOLG designed a prospective, randomized, multi-centre, phase-III trial (NARLAL2) for patients with LA-NSCLC. NARLAL2 (Novel Approach to Radiotherapy in Locally Advanced Lung cancer) is testing the hypothesis that inhomogeneous dose-escalation driven by the most FDG-avid regions will result in a higher loco-regional control at 30 months, without an increased risk of severe normal tissue complications, compared to a homogenous non-escalated standard treatment.

As part of the study protocol, both standard and dose-escalated treatment plans are produced for all patients, blinded to randomization. This provides a unique opportunity to examine the dose-escalation strategy on a patient specific level in a true clinical setting. We here describe the trial design and QA programme and report the dose planning results from the first thirty patients treated on trial, in terms of ability to dose escalate without increasing mean lung dose and without compromising dose constraints to other OARs.

Material and Methods

The NARLAL2 trial is currently recruiting patients with LA-NSCLC stage IIB-IIIB. It is a randomized, multi-centre, phase-III trial illustrated in Figure 1.

Target definition

A free-breathing FDG-PET scan and a 4D-CT scan with intravenous contrast are acquired for each patient in one or two imaging sessions, according to availability on site. The gross tumour volume (GTV) of the primary tumour is delineated as GTV-T and each malignant lymph node is delineated separately as GTV-Nx (x=1,2,…). Clinical target volumes (CTVs) are created with a 5 mm isotropic expansion of the GTVs, cropped with respect to bones, trachea and large blood vessels. Margins are added to create planning target volumes (PTVs), to ensure that the planned dose is delivered to the CTVs, taking into account uncertainties associated with planning and delivery of treatment[13]. The CTV-to-PTV margins are centre-specific, as they depend on the setup and image registration strategy applied. Respiratory motion is included in the patient-specific margins, either during delineation of the GTV [14] or as a part of the applied margin[15].

The FDG-scan is used to define optimisation volumes to drive dose-escalation and is rigidly registered to the 4D-CT scan. For each separate GTV (GTV-T and one or more GTV-Nx) larger than 4 cm^3, the peak standardised uptake (SUV_{peak}) value is determined as the average value of SUV in the continuous 1cm^3 with the highest SUV [16]. No background FDG-signal corrections are applied. Within the delineated GTVs, the GTV_{PET} is defined by the 50% of SUV_{peak} of the FDG signal within that specific GTV. If GTV-T is less than 4cm^3, the whole GTV-T is used to drive the dose-escalation. In contrast, if GTV-Nx is less than 4cm^3, then the lymph node is not an object for dose-escalation. Small GTV_{PET} volumes are expanded (by using 40% or 30% of SUV_{peak}), as outlined in Figure 2.

Treatment planning

The standard radiation regimen delivers 66 Gy in 33 Fractions (F), 5 days a week, homogenously to the PTV, ensuring that the minimum dose is 95% of 66 Gy. The escalated radiation regimen (also delivered in 33 F, 5 days a week) aims at a treatment plan where each GTV_{PET} receives the highest possible mean doses without exceeding a maximal mean dose of 95 Gy for GTV-T_{PET} and 74 Gy for GTV-Nx_{PET}, while keeping within dose limiting constraints for OARs. The PET volumes are used to drive a heterogeneous escalation of the GTVs and CTVs and thus no upper constraints are placed on target structures. Minimum delivered dose to PTV is 95% of 66 Gy.

Constraints for the maximum volume receiving x Gy (V_{xGy}) or the maximum dose to a volume of x cm^3 (D_{xcm3}) are applied to all OARs and are listed in Table 1.

A standard and a dose-escalated plan are produced for every patient, with the lung dose metrics achievable for the standard plan informing the dose-escalated plan: Maximum deviation for the escalated plan relative to the standard plan is 1 Gy for mean lung dose (MLD) and 2 percentage points for V_{20Gy} for that specific patient. To avoid bias in the treatment planning process, the randomization result is unknown to the treatment planner and the radiation oncologist until both standard and escalated plans are approved for clinical use.

Treatment planning is performed with inhomogeneity corrections, using advanced dose calculation algorithms and with advanced inverse-optimisation techniques (IMRT or VMAT).

Chemotherapy

All patients are treated with concomitant chemotherapy consisting of oral vinorelbine (50 mg three times weekly) and, if tolerable, two cycles of Cisplatin (75 mg/m^2) in week one and three. One or two cycles of induction chemotherapy, using a platinum doublet, are permitted.

Daily imaging and adaptation

Daily pre-treatment target position verification is done by 3D or 4D cone beam CT (CBCT) scans with primary tumour and/or malignant lymph node soft tissue registration. All participating centres are required to calculate local CTV to PTV margins sufficient to ensure dose coverage of the CTV given the centre-specific uncertainties. The acquired CBCT scans are used to systematically evaluate anatomical changes during the course of radiotherapy, and to assess the necessity of treatment adaptation in order to maintain target dose coverage and avoid over dosage of OARs. The CTV size is maintained in the adaptation process even when tumour shrinkage is present. To this end, all participating centres have guidelines for systematic adaptive treatment strategies.

Quality assurance

A detailed QA program has been used to ensure uniform planning and delivery processes among all participating centres. Compliance to this program was mandatory. The NEMA body phantom was scanned on all PET/CT scanners and the four largest spheres delineated according to protocol procedure and compared between scanners. The contouring algorithms employed for SUV threshold volume delineation were compared for two patient test cases. Consensus on target and OAR delineation was achieved by adopting the guidelines of [17,18] and a patient test case was delineated by all centres. Consensus on treatment planning was achieved in three test runs of 2-5 patient cases each. Finally, planning margins, daily imaging and adaptive strategies were presented and discussed at a mandatory workshop. After local trial initiation, a QA group consisting of two radiation oncologists and four medical physicists visit and evaluate each participating centre. Treatment of the first two patients at each centre is reviewed in detail (delineation, treatment planning, PTV margin, IGRT and adaptive strategies). Furthermore, each centre must expect to include at least five patients per year.

Sample size calculation

The primary trial endpoint is dose-escalation loco-regional control. A preliminary multi-centre treatment planning study, involving five Danish radiotherapy centres, indicated that an average dose-escalation of 14 Gy to the CTV was feasible, corresponding to 16 %-points improvement in loco-regional control at 30 months, using the tumour control probability model from [19]. Median loco-regional control in the control arm was assumed to be 36 months, based on data from standard clinical practice at Odense University Hospital (OUH). Median time for death without loco-regional progression (a competing, censoring event) was estimated at 43 months (data from OUH). The aim was 80% power to be able to reject the null hypothesis of equal hazard (HR=1) of loco-regional failure in the two arms, with 95% (two-sided) confidence. Patients are randomized 1:1 between the two arms over a five-year enrolment period, with one year of additional follow-up after enrolment closure. The trial sample size was based on Monte-Carlo simulations of possible outcomes of the study, taking the above points into account, and estimated that at least 150 patients should be included in each treatment arm. Accounting for 10% loss due to inclusion errors and missing follow-up, the study aims to include a total of 330 patients. Several interim analyses are planned for toxicity and overall survival, but none for the primary endpoint.

Data analysis

Standard and escalated plans for all patients are continually exported to a national DICOM-based radiotherapy plan database[20]. The current analysis considered pairs of plans for the first thirty patients enrolled (i.e. sixty plans in all), and dose-volume histograms (DVHs) were calculated for all structures for those patients. Selected dose metrics were extracted, summarized using medians and interquartile range (IQR, first to third quartile), and compared between standard and escalated plans using the Wilcoxon signed rank test.

Ethics

The study is approved by the Danish Research Ethics Committee (reg.no.43247) and is registred at clinicaltrials.gov (NCT02354274). All patients have given informed consent. Patients included in this analysis were randomized in the study. However, the results presented in the current analysis are from both the standard and escalated treatment plans, irrespective of randomization.

Results

The first thirty patients enrolled on the trial consisted of 20 females and 10 males, with a median age of 66 years (range 46 – 81), treated at three different radiotherapy centres. They were staged as IIB (1 patient), IIIA (16 patients), IIIB (12 patients) and recurrence (1 patient). The median (IQR) volume of the total GTV including primary tumour and lymph nodes was 54.8 cm^3 (25.8-100.8).

Four patients had no malignant lymph node targets, while two patients had only lymph node targets. The 28 patients with a primary tumour had median GTV-T_{PET} of 7.1 cm^3 (4.6-21.7), which was heterogeneously escalated to a mean dose of 93.9 Gy (90.0-94.6) in median. Dose-escalation above 90 Gy was not achieved in seven patients due to dose limiting OARs in close proximity to the primary tumour. The main dose-limiting organs were bronchi (1 patient), thoracic wall (3 patients), and connective tissue (3 patients). The 26 patients with lymph node involvement had a total of 96 lymph node targets, but only 26 nodes were large enough for escalation (GTV-Nx > 4 cm^3). The FDG-avid volumes of the 26 escalated lymph nodes achieved a median mean dose of 73.0 Gy (71.6-73.7). Four escalated lymph nodes in two patients achieved

mean doses of less than 71 Gy with dose limiting organs being bronchi (1 patient) and connective tissue (1 patient). The FDG-volumes drove a heterogeneous escalation of the GTVs and CTVs (see DVHs for GTV_{PET}, GTV, CTV and PTV for one patient in Figure 3, panel a and b). The resulting escalated mean doses to GTV-T and GTV-N were in median 87.5 Gy (84.1-90.8) and 71.8 Gy (70.3-72.4), compared to 66.5 Gy (66.3-66.9) and 66.8 Gy (66.4-67.0), respectively in the standard arm. Corresponding mean doses to CTV-T and CTV-N were 81.3 Gy (78.0-83.4) and 70.9 Gy (69.6-71.6) in the escalated arm, compared to 66.5 Gy (66.2-66.8) and 66.7 Gy (66.4-67.0) in the standard arm.

The dose metrics for OARs for the standard and escalated plans were compared (presented for one patient in Figure 3, panel c and d). The DVHs were very similar, but focusing on doses above 60 Gy reveals increment in volumes receiving doses of 66-72 Gy for the escalated plan.

The median dose metrics values of different OAR revealed no statistically significant differences in mean doses to the heart and the lung, and V_{35Gy} of oesophagus, for the standard and dose-escalated treatment plans (Table 2). In contrast, dose to small high dose regions (D_{1cc}) in oesophagus, bronchi, heart, trachea, aorta, thoracic wall and connective tissue were all statistically significantly larger for the dose-escalated treatment plans.

Six patients received an adaptive plan during the treatment course. The reasons for plan adaptation were pleural effusion (1 patient), deformation of primary tumour (2 patients), baseline shift between primary tumour and lymph nodes (1 patient), atelectasis (1 patient), and tumour shrinkage (1 patient).

Discussion

This study demonstrates the feasibility of conducting a dose-escalation trial for locally advanced NSCLC in a multi-centre setting with application of a strict QA programme. The first thirty patients on trial all complied with the treatment planning criteria, and no violations of the normal tissue constraints were observed. The pre-randomization treatment planning procedure, yielding standard and escalated plans for all patients, allowed for analysis of the impact of the dose-escalation strategy on an individual patient level. It demonstrated a large increase in tumour dose for all patients if randomized to the experimental arm.

The current study is based on a fundamental strategy of heterogeneous irradiation of the tumour volume, where the dose-escalation is driven by the most FDG-avid tumour areas. No objectives on target dose outside the FDG-avid areas are made, except for basic coverage with standard prescription dose. This allows for mean doses to the FDG-avid areas of GTV-T of 94 Gy/33 F (median value), without increasing MLD or violating the conservative OAR constraints. The trial is designed to have MLD +/-1Gy between the standard and dose-escalated arms, which results in statistically equivalent MLD in the two arms. An equal risk of lung toxicity in the two arms is thus expected[21]. Since only large lymph nodes (> 4 cm^3) are escalated, the majority of the lymph nodes (73%) were prescribed the standard 66 Gy/33 F. The FDG-avid volumes of the remaining large lymph nodes were in median escalated to 73 Gy in mean dose.

Dose-escalation driven by the PET-avid regions instead of the entire target volume is based on studies of loco-regional recurrence patterns[7,8]. However, there is currently no prospective evidence available to support the hypothesis that increased dose to the PET-avid areas will result in better local control, compared to either standard treatment or dose-escalation of the whole PTV. The Dutch phase-II PET-boost trial [22] examined part of this question, randomizing between isotoxic dose-escalation of the entire PTV

and dose-escalation of only the FDG-avid tumour areas expanded with an uncertainty margin. The NARLAL2 trial employs a hybrid approach, where dose-escalation of the entire PTV is not pursued, but not actively prevented either. This strategy resulted in high mean doses to GTV-T and CTV-T of 87 and 81 Gy, respectively, in this initial trial cohort of thirty patients.

Radiation dose-escalation in NSCLC is a contentious issue, and the results of the RTOG-0617 trial - where 60 Gy proved to be better than 74 Gy in terms of overall survival[4] - questioned fundamental assumptions about dose-response for local control. The results of RTOG-0617 are still being investigated and debated, but care should unquestionably be taken if dose-escalation is pursued. RTOG-0617 stratified for treatment technique, 3D-CRT versus IMRT, and secondary analyses report that treatment technique significantly affected the risk of toxicity and patient-reported quality of life[11,23]. No interaction between treatment technique and impact of dose-escalation has been reported, and consequently there is no guarantee that the use of IMRT allows for safe delivery of high-dose radiotherapy. Nevertheless, RTOG-0617 data demonstrated the importance of high quality in technical treatment delivery for this patient group. The current NARLAL2 trial has, in the treatment planning procedures and the pre- and on-trial QA processes, paid close attention to high-quality treatment plan optimization and compliance with dose constraints for the OARs. All relevant OARs are delineated, including all mediastinal connective tissue. Normal tissue constraints used are consistently conservative, especially with regards to mediastinal structures. No large >74 Gy hotspots are allowed, which appears to be a safe dose level for the aorta[24], the bronchi and the trachea[25,26], as well as for the thoracic wall and other connective tissues[25]. Dose constraints to the oesophagus have been much debated, with most publications on dose metric predictors concentrating on acute toxicity, but severe late toxicity such as strictures may primarily be related to high dose volumes[27], and therefore a conservative dose limit of 70 Gy was chosen for the trial. Data on cardiac toxicity after radiotherapy for NSCLC is currently emerging[11,28], with no clear agreement on dose constraints to be used in clinical practice. The treatment plan data reported in the current study demonstrates the lack of significant differences between doses to OARs in the two arms - except in the case of comparatively small volumes receiving dose in the range 66-74 Gy. Small volumes of lung tissue may receive higher dose (>74 Gy), but experience from stereotactic lung radiotherapy indicates that this is generally well-tolerated.

While careful attention to pre-treatment dose planning is undoubtedly important, anatomical changes during RT can cause the delivered dose to tumour and malignant lymph nodes as well as to OARs to deviate substantially from the planned dose[29,30]. This introduces high risk of under dosage of the tumour and lymph nodes and over dosage of OARs, where the latter represents a much more severe problem in the case of dose-escalation. To ensure that the planned dose is actually delivered, each participating centre has implemented an adaptive strategy prior to patient enrolment. Twenty percent of the first trial patients were re-planned during the treatment course, clearly demonstrating the need for such policies.

In conclusion, the dosimetric results of the first thirty patients treated in the NARLAL2 trial confirmed that FDG-driven dose-escalation can achieve significantly increased tumour doses without compromising dose constraints to OARs. The feasibility is proven in daily clinical practice in a multi-centre setting. At the time of submission, 82 patients have been enrolled and the trial is open for enrolment in 4 centres.

Acknowledgements

Conflict of interest statement

The trial is supported by a small, unrestricted grant from Pierre Fabre. Pierre Fabre had no involvement in study design, writing of the manuscript, data collection, analysis, or interpretation. The trial is not testing pharmaceuticals, but compares two radiotherapy regimes.

Figure Captions

Figure 1: Study design of the NARLAL2 trial. Patients are randomized 1:1 between standard and dose-escalated radiation regimens, with dose-escalation driven by the most FDG-avid regions of the primary tumour and lymph nodes. All patients will have treatment plans for both arms approved for clinical use before the randomization result is known to prevent any bias in the dose planning. Daily treatment is image-guided, with centre-specific treatment margins and adaptive treatment strategies.

Figure 2: Definition of FDG-avid areas used to drive dose-escalation. For a GTV-T smaller than 4 cm^3 the whole GTV-T is used, while for a GTV-Nx smaller than 4 cm^3 no dose-escalation is pursued. For all GTVs larger than 4 cm^3, GTV_{PET} (dotted black line) is defined as the 50% of the SUV_{peak} from the PET-signal within that specific GTV. However, if the GTV_{PET} is less than 4 cm^3 or less than 30% of the GTV (for each specific GTV), first the 40% of the SUV_{peak}, then the 30% of the SUV_{peak} is utilised. If the GTV_{PET} is still too small, then an isotropic margin is added until the volume requirements are fulfilled.

Figure 3: As an example, DVH's for one patient is displayed. The four panels have different scales on the axes. DVHs with solid lines for the standard plan and dashed lines for the escalated plan. Panel a and b display DVH's (PTV, CTV, GTV and GTV_{PET}) for the primary tumour and the composite lymph nodes. Panel c displays the full DVH of selected OARs (Bronchi, Oesophagus and lung) with relative volumes, while panel d displays the absolute volume receiving doses above 60 Gy for the Oesophagus and Bronchi.

References

[1] Auperin A, Le PC, Rolland E et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181-90.

[2]Machtay M, Bae K, Movsas B et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 2012;82:425-34.

[3] Kong FM, Ten Haken RK, Schipper MJ et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose-escalation study. Int J Radiat Oncol Biol Phys 2005;63:324-33.

[4] Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomized, two-by-two factorial phase 3 study. Lancet Oncol.2015; 16:187-199.

[5] Schwarz M, Alber M, Lebesque JV, Mijnheer BJ, Damen EM. Dose heterogeneity in the target volume and intensity-modulated radiotherapy to escalate the dose in the treatment of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2005;62:561-70.

[6] Nielsen TB, Hansen O, Schytte T, Brink C. Inhomogeneous dose-escalation increases expected local control for NSCLC patients with lymph node involvement without increased mean lung dose. Acta Oncol 2014;53:119-25.

[7] Abramyuk A, Tokalov S, Zophel K et al. Is pre-therapeutical FDG-PET/CT capable to detect high risk tumor subvolumes responsible for local failure in non-small cell lung cancer? Radiother Oncol 2009; 91:399-404.

[8] Aerts HJ, van Baardwijk AA, Petit SF et al. Identification of residual metabolic-active areas within individual NSCLC tumours using a pre-radiotherapy (18)Fluorodeoxyglucose-PET-CT skan. Radiother Oncol;91:386-92.

[9] Schytte T, Nielsen TB, Brink C, Hansen O. Pattern of loco-regional failure after definitive radiotherapy for non-small cell lung cancer. Acta Oncol. 2014; 53:336-41.

[10] van Diessen JN, Chen C, van den Heuvel MM, Belderbos JS, Sonke JJ. Differential analysis of local and regional failure in locally advanced non-small cell lung cancer patients treated with concurrent chemoradiotherapy. Radiother Oncol. 2016;118:447-52.

[11] Chun SG, Hu C, Choy H et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. J Clin Oncol. 2017;35:56-62.

[12] Hansen O, Knap MM, Khalil A et al. A randomized phase II trial of concurrent chemoradiation with two doses of radiotherapy, 60 Gy and 66 Gy, concomitant with a fixed dose of oral vinorelbine in locally advanced NSCLC (Submitted to Radiother Oncol)

[13] van Herk M. Errors and margins in radiotherapy. Semin Radiat Oncol. 2004;14:52-64.

[14] Underberg RW, Lagerwaard FJ, Slotman BJ, Cuijpers JP, Senan S. Use of maximum intensity projections (MIP) for target volume generation in 4DCT scans for lung cancer. Int J Radiat Oncol Biol Phys. 2005;63:253-60.

[15] Wolthaus JW, Schneider C, Sonke JJ, van Herk M, Belderbos JS, Rossi MM, Lebesque JV, Damen EM. Mid-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. Int J Radiat Oncol Biol Phys. 2006;65:1560-71.

[16] Lodge MA, Chaudhry MA, Wahl RL. Noise considerations for PET quantification using maximum and peak standardized uptake value. J Nucl Med 2012;53:1041-7.

[17] Kong FM, Ritter T, Quint DJ et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 2011;81:1442-57.

[18] Feng M, Moran JM, Koelling T et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys 2011;79:10-8.

[19] Martel MK, Ten Haken RK, Hazuka MB et al. Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients. Lung Cancer 1999;24:31-7.

[20] Westberg J, Krogh S, Brink C, Vogelius IR. A DICOM based radiotherapy plan database for research collaboration and reporting. J Phys. 2014; 489.

[21] Marks LB, Bentzen SM, Deasy JO et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys. 2010; 76:S70-S76.

[22] van Elmpt W, De Ruysscher D, van der Salm A et al. The PET-boost randomised phase IIdose-escalation trial in non-small cell lung cancer. Radiother Oncol. 2012; 104:67-71.

[23] Movsas B, Hu C, Sloan J, Bradley J et al. Quality of Life Analysis of a Radiation Dose-Escalation Study of Patients With Non-Small-Cell Lung Cancer: A Secondary Analysis of the Radiation Therapy Oncology Group 0617 Randomized Clinical Trial. JAMA Oncol. 2016;2:359-67.

[24] Evans JD, Gomez DR, Amini A et al. Aortic dose constraints when reirradiating thoracic tumors. Radiother Oncol 2013;106:327-32

[25] Socinski MA, Blackstock AW, Bogart JA et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. J Clin Oncol 2008;26:2457-63.

[26] Cannon DM, Mehta MP, Adkison JB et al. Dose-limiting toxicity after hypofractionated dose-escalated radiotherapy in non-small-cell lung cancer. J Clin Oncol. 2013;31:4343-8.

[27] Chen C, Uyterlinde W, Sonke JJ, de Bois J, van den Heuvel M, Belderbos J. Severe late esophagus toxicity in NSCLC patients treated with IMRT and concurrent chemotherapy. Radiother Oncol. 2013;108:337-41.

[28] Wang K, Eblan MJ, Deal AM et al. Cardiac Toxicity After Radiotherapy for Stage III Non-Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy. J Clin Oncol. 2017 Epub ahead of print.

[29] Møller DS, Holt MI, Alber M et al. Adaptive radiotherapy for advanced lung cancer ensures target coverage and decreases lung dose. Radiother Oncol. 2016;121:32-38.

[30] Sibolt P, Ottosson W, Sjöström D, Larsen C, Behrens CF. Adaptation requirements due to anatomical changes in free-breathing and deep-inspiration breath-hold for standard and dose-escalated radiotherapy of lung cancer patients. Acta Oncol. 2015;54:1453-60.